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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Ernest J. Lee, et al.	**Examiner:**	Schlientz, Nathan
Serial No.:	10/626,275	**Art Unit:**	1616
Filed:	July 24, 2003	**Atty Docket:**	PC28017
Title:	PRAMIPEXOLE ONCE-DAILY DOSAGE FORM		

DECLARATION OF JOHN M. HEIMLICH UNDER 37 C.F.R. §132

I, John M. Heimlich , declare that:

1. I am currently a Senior Principal Scientist at Pfizer, Ltd., Sandwich UK, where I have been employed since 2006. Pfizer Inc. is the owner of this patent application, which it acquired through acquisition of Pharmacia Corp., where I was employed at the time of the patent filing. My employment with Pfizer and legacy organizations (Pharmacia, Pharmacia & Upjohn) has been continuous since 1997, and I have been working in solid formulation development with an emphasis on modified release dosage forms and hydrophilic matrix tablets during that time. I have an undergraduate B.S. Pharmacy degree from The Ohio State University (1992), and a Ph. D. in Industrial and Physical Pharmacy from Purdue University, which was obtained in 1997.

2. I have studied the present patent application, as well as certain publications referred to in the Office Action of November 12, 2009. My declaration relates to those publications.

3. I understand that Holman, U.S. Patent 6,277,875 has been cited as a prior art reference. I also understand that one basis for rejection, though not solely relied on by the Examiner, is that Holman may describe a composition of pramipexole with other excipients, including pregelatinized starch and hydroxypropyl methylcellulose which inherently possesses the sustained release profile of the invention.

4. The invention of the present application relates to a sustained release pramipexole formulation having defined sustained release parameters and comprising, among other ingredients, a starch and a hydrophilic polymer. I understand that accompanying my declaration is an amendment to the claims such that they now recite that the pramipexole is in the dihydrochloride monohydrate form, and that the formulation comprises about 20-70% of hydrophilic polymer and about 25 to

75% starch. The claims further state, as amended, that the pramipexole is dispersed in hydrophilic polymer and that hydrophilic polymer functions to provide sustained release.

5. I do not read Holman to disclose such a composition. In particular, I do not believe Holman discloses a sustained release composition, but instead only discloses an immediate release tablet.

6. Holman discloses at column 11, line 42, a tablet containing as inactive ingredients lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxyl propylmethyl cellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide and polysorbate 80. This description reads to me, and I believe to anyone skilled in this art, as a film coated immediate release tablet. In particular, all ingredients listed in the first part of the formulation from "lactose" to "magnesium stearate" are typical components of the core of an immediate release tablet (lactose and starch are typical carriers, microcrystalline cellulose is a binding agent, sodium starch glycolate is a disintegrant and magnesium stearate is a lubricant). The remaining ingredients in the description, from "purified water" to "polysorbate 80", are typical film coating ingredients.

7. I have attached a copy of a page from R.C. Rowe et al. (Eds.), *Handbook of Pharmaceutical Excipients*, Pharmaceutical Press, London, UK (2003), which states that sodium starch glycolate is "widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations" (see p. 581, col. 1, next to last paragraph). The presence of sodium starch glycolate is not consistent with a pharmaceutical formulation having sustained release properties as claimed.

8. Holman also differs in that while it mentions hydroxypropyl methylcellulose, this is in connection with a film coating. In the present invention of an extended release composition, hydrophilic polymer (e.g. HPMC) in the composition provides, at least in part, for sustained release of pramipexole. I understand that the claims have been clarified in that they now recite that the pramipexole is dispersed in hydrophilic polymer; this differs substantially from Holman, which does not disclose pramipexole dispersed in HPMC (hydrophilic polymer). The claims have also been clarified to recite that hydrophilic polymer functions to provide sustained release, another significant difference from the Holman composition.

9. For at least these reasons, I do not believe that the Holman pramipexole composition inherently possesses the sustained release characteristics of the instant invention. Nor are other parameters of the instant claims as amended met, as pointed out above.

10. I understand that the Examiner has indicated that if Holman does not describe the invention, Pospisilik '240 (U.S. 2002/0103240) and Vandecruys (WO 00/59477) nevertheless provide the teachings that would be necessary to modify Holman to arrive at the invention with a reasonable expectation of success. I do not believe this to be the case.

11. Pospisilik '240 describes a process for resolving pramipexole into enantiomers. The only disclosure I am able to discern in Pospisilik relevant to the present invention is the statement at ¶64 that controlled release formulations may be produced containing pramipexole and a "suitable" release controlling agent comprising water and/or a water-insoluble macromolecular substance such as an acrylate polymer or a modified cellulose.

12. This statement does not suggest to me that one would be able, with a reasonable expectation of success, to arrive at a sustained release formulation of pramipexole comprised of about 20-

70% of hydrophilic polymer and about 25 to 75% starch, wherein the pramipexole is dispersed in hydrophilic polymer which functions to provide sustained release, and wherein the composition when administered once daily exhibits bioavailability substantially equivalent to an equal daily dose of immediate release pramipexole administered three times a day. I do not see any indication of such a composition, or that it would be able to achieve such a result.

13. The Action appears to be relying on the Vandecruys reference to provide teachings missing from Holman and Pospisilik '240. The Vandecruys reference relates to controlled release compositions containing pregelatinized starch to prevent dose dumping, including those compositions wherein pregelatinized starch is combined with a hydrophilic polymer. The Action notes that the reference lists "anti-Parkinsonian drugs" as one type of drug that may be so formulated. The Action also points to a specific disclosure in Vandecruys of an example of a pharmaceutical formulation at Table 5 which displays release of the active ingredient at rates within the ranges recited in the current claims.

14. I do not read the Vandecruys reference to suggest making a sustained release formulation of pramipexole comprise of about 20-70% of hydrophilic polymer and about 25 to 75% starch, wherein the pramipexole is dispersed in hydrophilic polymer which functions to provide sustained release, wherein the composition when administered once daily exhibits bioavailability substantially equivalent to an equal daily dose of immediate release pramipexole administered three times a day. I also do not read this reference as providing any reasonable expectation of success that such a formulation would be successful.

15. The Vandecruys reference does not describe pramipexole (it only lists the anti-Parkinsonian agents bromocryptine mesylate, levodopa, and selegiline).

16. The Example pointed out by the Action, at Table 5, relates to Tablet 6, described at page 26. Tablet 6 contains the active agent 3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridine-2(1H)-yl]ethyl]-2-methl-4H-pyrido[1,2-a]pyrimidin-4-one in a formulation which also contains cyclodextrin and lactose monohydrate. Cyclodextrin is normally added to a formulation to form a complex with poorly soluble active materials. Lactose monohydrate is normally added to aid in release of poorly soluble materials.

17. 3-[2-[3,4-dihydrobenzofuro[3,2-c]pyridine-2(1H)-yl]ethyl]-2-methl-4H-pyrido[1,2-a]pyrimidin-4-one is chemically distinct from pramipexole. Based on the use of appreciable quantities of both cyclodextrin and lactose monohydrate in the Vandecruys reference, I understand the formulation of Tablet 6 to relate to an extended release composition of a poorly soluble active.

18. I do not understand this disclosure to provide any indication of whether such a formulation, or any one which is similar, would or could provide the same sustained release properties for pramipexole. Pramipexole is highly soluble (about 20 mg/ml at 20-25°C). Such drugs can be difficult to formulate in sustained release dosage forms. The formulation of Tablet 6 provides little or nothing that could predict whether the instantly claimed formulation would exhibit the claimed properties.

19. I do not see any other disclosure in the Vandecruys reference which remedies such deficient teachings.

20. For this reason, I do not read Vandecruys to provide the teachings missing from Holman and Pospisilik to arrive at the present invention.

21. I further declare that all statements made herein of my own knowledge are true and that all statements made on information are believed to be true; and further that these statements were made with the knowledge that willful false statements and the likes made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

11 MAY 2010

Date

Dr. John M. Heimlich